IN THE SPECIFICATION:

Please amend paragraph **[0034]** as follows:

[0034] In particular, it is provided to perform a process according to the invention further including a step c) comprising determining the presence of the gene product in or derived from a cell which has not been contacted with the oligopeptide, or a modification or derivative thereof, and determining the ratio of gene product found in step b to gene product found in step c, as can easily been done with the present-day ~~genechip~~ GENECHIP® array technology (see, for example, the detailed description herein) and related methods of expression profiling known in the art.

Please amend paragraph **[0035]** as follows:

[0035] Another method provided herein for identifying or obtaining information on a ~~signalling~~ signaling molecule (or for that matter the ~~signalling~~ signaling molecule itself, considering that the next step of synthesizing the molecule, generally being a short peptide, is ~~whole~~ wholly within the art) comprising a peptide or functional derivative or analogue thereof capable of modulating expression of a gene in a cell comprises providing the cell with a peptide or derivative or analogue thereof and determining relative up-regulation and/or down-regulation of at least one gene expressed in the cell. The up-regulation can classically be studied by determining via, for example, Northern or Western blotting or nucleic acid detection by PCR or immunological detection of proteins whether a cell or cells make more (in the case of up-regulation) or less (in the case of down-regulation) of a gene expression product such as mRNA or protein after the cell or cells have been provided with the peptide or derivative or analogue thereof. Of course, various methods of the invention can be combined to better analyze the functional analogue of the peptide or derivative or analogue under study. Furthermore, relative up-regulation and/or down-regulation of a multitude or clusters of genes expressed in the cell can be easily studied as well, using libraries of positionally or spatially addressable predetermined or known relevant nucleic acid sequences or unique fragments thereof bound to an array or brought in an array format, using for example a nucleic acid library or so-called ~~genechip~~ GENECHIP® array expression analysis systems. Lysates of cells or preparations of cytoplasma and/or nuclei of cells that have been provided with the peptide or derivative or analogue under

study are then contacted with the library and relative binding of, for example, mRNA to individual nucleic acids of the library is then determined, as further described herein in the detailed description.

Please amend paragraph **[0112]** as follows:

[0112] FIGS. 36-47. Effect of NMPF on septic shock syndrome in Rhesus monkeys. On the time point 70 minutes, *E. coli* was infused and at the end of *E. coli* infusion (time point 190 minutes), ~~the antibiotic Baytril~~ BAYTRIL® antibiotic was injected. The control monkey (monkey 429) was treated with 0.9% NaC1 at the time point of 100 minutes, whereas the NMPF treated monkeys (monkey 459 and 427) received the NMPF treatment at the same time point as the control monkey. Heart rate (beats per minute), blood pressure (mmHg), difference between systolic and diastolic blood pressure and blood oxygen concentration (saturation in %) of the control monkey 429 (FIGS. 36-39), NMPF treated monkeys 459 (FIGS. 40-43) and 427 (FIGS. 44-47) in the time (minutes) during the experiment are shown.

Please amend paragraph **[0122]** as follows:

[0122] The peptides as mentioned in this document such as LQG, AQG, LQGV (SEQ ID NO:1), AQGV (SEQ ID NO:2), LQGA (SEQ ID NO:19), VLPALP (SEQ ID NO:13), ALPALP (SEQ ID NO:21), VAPALP (SEQ ID NO:22), ALPALPQ (SEQ ID NO:23), VLPAAPQ (SEQ ID NO:24), VLPALAQ (SEQ ID NO:25), LAGV (SEQ ID NO:26), VLAALP (SEQ ID NO:27), VLPALA (SEQ ID NO:28), VLPALPQ (SEQ ID NO:29), VLAALPQ (SEQ ID NO:30), VLPALPA (SEQ ID NO:31), GVLPALP (SEQ ID NO:32), VVCNYRDVRFESIRLPGCPRGVNPVVSYAVALSCQCAL (SEQ ID NO:35), RPRCRPINATLAVEKEGCPVCITVNTTICAGYCPT (SEQ ID NO:45), SKAPPPSLPSPSRLPGPS (SEQ ID NO:38), LQGVLPALPQVVC (SEQ ID NO:34), SIRLPGCPRGVNPVVS (SEQ ID NO:39), LPGCPRGVNPVVS (SEQ ID NO:40), LPGC (SEQ ID NO:41), MTRV (SEQ ID NO:42), MTR, and VVC were prepared by solid-phase synthesis (Merrifield, 1963) using the fluorenylmethoxycarbonyl (Fmoc)/tert-butyl-based methodology (Atherton, 1985) with 2-chlorotrityl chloride resin (Barlos, 1991) as the solid support. The side-chain of glutamine was protected with a trityl function. The peptides were synthesized

manually. Each coupling consisted of the following steps: (i) removal of the alpha-amino Fmoc-protection by piperidine in dimethylformamide (DMF), (ii) coupling of the Fmoc amino acid (3 eq) with diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) in DMF/N-methylformamide (NMP) and (iii) capping of the remaining amino functions with acetic anhydride/diisopropylethylamine (DIEA) in DMF/NMP. Upon completion of the synthesis, the peptide resin was treated with a mixture of trifluoroacetic acid (TFA)/H_2O/triisopropylsilane (TIS) 95:2.5:2.5. After 30 minutes, TIS was added until decolorization. The solution was evaporated *in vacuo* and the peptide precipitated with diethylether. The crude peptides were dissolved in water (50-100 mg/ml) and purified by reverse-phase high-performance liquid chromatography (RP-HPLC). HPLC conditions were: column: ~~Vydac~~ VYDAC® column TP21810C18 (10 x 250 mm); elution system: gradient system of 0.1% TFA in water v/v (A) and 0.1% TFA in acetonitrile (ACN) v/v (B); flow rate 6 ml/minute; absorbance was detected from 190-370 nm. There were different gradient systems used. For example for peptides LQG and LQGV (SEQ ID NO:1): 10 minutes 100% A followed by linear gradient 0-10% B in 50 minutes. For example for peptides VLPALP (SEQ ID NO:3) and VLPALPQ (SEQ ID NO:29): 5 minutes 5% B followed by linear gradient 1% B/minute. The collected fractions were concentrated to about 5 ml by rotation film evaporation under reduced pressure at 40°C. The remaining TFA was exchanged against acetate by eluting two times over a column with anion exchange resin (~~Merck~~ MERCK® II exchange resin) in acetate form. The eluate was concentrated and lyophilized in 28 hours. Peptides later were prepared for use by dissolving them in PBS.

Please amend paragraph **[0128]** as follows:

[0128] A reverse-phase high-performance liquid chromatography (RP-HPLC) method was used to prove the presence of synthetic oligopeptide in the nuclear extracts. We used a Shimadzu HPLC system equipped with ~~Vydac~~ VYDAC® monomeric C18 column (column 218MS54, LC/MS C18 reversed phase, 300A, 5 μm, 4.6 mm ID x 250 mm L); elution system: gradient system of 0.01% TFA and 5% acetonitrile (CAN) in water v/v (A) and 0.01% TFA in 80% acetonitrile (ACN) v/v (B); flow rate 0.5 ml/minute; absorbance was detected from 190-370 nm. The gradient time program was as follows:

Please amend paragraph **[0132]** as follows:

[0132] *Sepsis.* For the endotoxin model, BALB/c mice were injected i.p. with 8-9 mg/kg LPS (*E. coli* 026:B6; Difco Lab., Detroit, MI, USA). Control groups (PBS) were treated with PBS i.p. only. To test the effect of NMPF from different sources (synthetic, commercial hCG preparation [c-hCG]), we treated BALB/c mice with a dose of 300-700 IU of different hCG preparations (PG23; ~~Pregnyl~~ PREGNYL® hCG batch no. 235863, PG25; ~~Pregnyl~~ PREGNYL® hCG batch no. 255957) and with synthetic peptides (5 mg/kg) after two hours of LPS injection. In other experiments, BALB/c mice were injected i.p. either with 10 mg/kg or with 11 mg/kg LPS (*E. coli* 026:B6; Difco Lab., Detroit, MI, USA). Subsequently, mice were treated after 2 hours and 24 hours of LPS treatment with NMPF peptides.

Please amend paragraph **[0134]** as follows:

[0134] *Sepsis* experiments. To determine the effect of synthetic peptides (NMPF) in high-dose LPS shock model, BALB/c mice were injected intraperitoneally with different doses of LPS and survival was assessed daily for 5 days. In this experiment (for the LPS endotoxin model), BALB/c mice were injected i.p. with 8-9 mg/kg LPS (*E. coli* 026:B6; Difco Lab., Detroit, MI, USA). Control groups (PBS) were treated with PBS i.p. only. We treated BALB/c mice with a dose of 300-700 IU of different hCG preparations (PG23; ~~Pregnyl~~ PREGNYL® hCG batch no. 235863, PG25; ~~Pregnyl~~ PREGNYL® hCG batch no. 255957) or with peptides (5 mg/kg) after two hours of LPS injection.

Please amend paragraph **[0145]** as follows:

[0145] Nine days after culture initiation, non-adherent cells were collected and counted with a ~~Coulter~~ COULTER® Counter (Coulter).

Please amend paragraph **[0170]** as follows:

[0170] In order to determine whether NMPF has effect on the disease development in NOD mice, we tested NMPF on pre-diabetic female NOD mice at the age of 13-14 weeks. After only two weeks of treatment (injection of NMPF (5 mg/kg) every other day), glucosuria data of all NOD mice was analyzed at the age of 17 weeks. Profound anti-diabetic effect (mice negative

for glucosuria) was observed in different NMPF groups as compared to the PBS group, especially in NMPF groups treated with peptide VLPALPQVVC (SEQ ID NO:20), VLPALP (SEQ ID NO:3), MTRV (SEQ ID NO:42), LPGCPRGVNPVVS (SEQ ID NO:40) and LPGC (SEQ ID NO:41). In addition, impairment of the glucose tolerance test was positively correlated to insulitis, but negatively correlated to the number of functional beta cells; also this test showed that NOD mice successfully treated with NMPF were tolerant for glucose as compared to the PBS group. Our results show that PBS treated NOD mice were all diabetic at the age of 23 weeks. Whereas, NOD mice treated three times a week for two weeks with NMPF showed profound inhibition of diabetes development. The strongest anti-diabetic effects were seen with NMPF-1, -4, -5, -6, -7, -65, -66 and commercial hCG preparation (~~Pregnyl~~ PREGNYL® hCG, Organon, Oss, The Netherlands, batch no. 235863). These mice had a low fasting blood glucose level and were tolerant for glucose (data partially shown). However, NMPF-71 showed no effect on the incidence of diabetes, while NMPF-64 and NMPF-11 had a moderate anti-diabetic effect.

Please amend paragraph **[0261]** as follows:

[0261] Antibiotic was used to synchronize the shock induction in the monkeys. ~~Baytril~~ BAYTRIL® antibiotic (~~Baytril~~ BAYTRIL® antibiotic 2.5%, Bayer, Germany) was used instead of gentamycin, as the strain proved only marginally susceptible to the latter antibiotic.

Please amend paragraph **[0267]** as follows:

[0267] *Antibiotics.* ~~Baytril~~ BAYTRIL® antibiotic was administered intravenously immediately after completion of the two-hour *E. coli* infusion (i.v.; dose 9 mg/kg).

Please amend paragraph **[0272]** as follows:

[0272] *Monkey 429(control).* Female monkey (5.66 kg) received an i.v. injection of *E. coli* 086 (10E10 CFU/kg). In a dose titration study with this batch performed in 1991, this bacterial dose induced lethal shock within 8 hours after the start of the infusion. The infusion period was 2 hours. ~~Baytril~~ BAYTRIL® antibiotic was administered intravenously immediately after completion of the two-hour *E. coli* infusion (i.v.; dose 9 mg/kg). After the *E. coli* injection, the monkey was observed by the authorized veterinarian without knowing which of the monkeys

received NMPF treatment. The clinical observations were as follows: vomiting, undetectable pulse, heart ~~arythmia~~ arrhythmia, abnormalities in ECG: signs of ventricle dilatation/heart decompensation (prolonged QRS complex, extra systoles), decreased blood clotting and forced respiration. In addition, there was a big fluctuation in heart rate (30-150 beats per minute), collapse of both systolic and diastolic blood pressure (35/20 mmHg), and decrease in blood oxygen concentration (80-70%). Seven hours after the start of the *E. coli* infusion, monkey began to vomit blood and feces, and have convulsions. After final examination, the veterinarian did not give permission to let this monkey awake. At this time point, the control monkey was euthanized. Hereafter, post-mortem examination was conducted and internal organs were examined *in situ*. A number of internal bleedings were found by the pathologist.

Please amend paragraph **[0273]** as follows:

[0273] *Monkey 459(*NMPF*)*. Female monkey (5.44 kg) received an i.v. injection of *E. coli* 086 (10E10 CFU/kg). In a dose titration study with this batch performed in 1991, this bacterial dose induced lethal shock within 8 hours after the start of the infusion. The infusion period was 2 hours. Thirty minutes after the initiation of *E. coli* infusion, NMPF was i.v. injected in a single bolus injection. ~~Baytril~~ BAYTRIL® antibiotic was administered intravenously immediately after completion of the two-hour *E. coli* infusion (i.v.; dose 9 mg/kg). After the *E. coli* injection, this monkey was also observed by the authorized veterinarian without knowing which of the monkeys received NMPF treatment. The clinical observations were as follows: normal pulse, heart sounds normal, normal ECG, higher heart-rate but otherwise stable (180 beats per minute), no hypotension (75/30 mmHg), normal blood oxygen concentration (95-85%), lungs sound normal, and normal turgor. Seven hours after the start of the *E. coli* infusion, the clinical condition of the monkey was stable. After final examination, the veterinarian did give permission to let this monkey awake due to her stable condition. In order to compare the hematological and immunological parameters between the control and NMPF-treated monkey, at this time point the NMPF-treated monkey 459 was euthanized. Hereafter, post-mortem examination was conducted and internal organs were examined *in situ*. No macroscopic internal bleedings were found by the pathologist.

Please amend paragraph **[0274]** as follows:

[0274] *Monkey 427(NMPF).* Female monkey (4.84 kg) received an i.v. injection of *E. coli* 086 (10E10 CFU/kg). In a dose titration study with this batch performed in 1991, this bacterial dose induced lethal shock within 8 hours after the start of the infusion. The infusion period was 2 hours. Thirty minutes after the initiation of *E. coli* infusion, NMPF was i.v. injected. ~~Baytril~~ BAYTRIL® antibiotic was administered intravenously immediately after completion of the two-hour *E. coli* infusion (i.v.; dose 9 mg/kg). After the *E. coli* injection, this monkey was also observed by the authorized veterinarian ~~doctor~~ without knowing which of the monkeys received NMPF treatment. The clinical observations were as follows: normal pulse, heart sounds normal, normal ECG, moderately higher heart-rate but otherwise stable (160 beats per minute), no hypotension (70/30 mmHg), normal blood oxygen concentration (95-90%), lungs sound normal, and normal turgor. Seven hours after the start of the *E. coli* infusion, the clinical condition of the monkey was stable. After final examination, the veterinarian did give permission to let this monkey wake up due to her stable condition. Monkey woke up quickly, she was alert and there was a slow disappearance of edema.

Please amend paragraph **[0275]** as follows:

[0275] PM1 T-cell line was obtained from American Type Culture Collection (Manassas, VA) and was cultured at 37°C in 5% CO_2. These cells were maintained and cultured in RPMI 1640, 10% fetal bovine serum, 2 mM L-glutamine, and antibiotics penicillin and streptomycin. For genomic experiments, cells (2 x 10^6/ml) were incubated with phytohemagglutinin (PHA, 10 µg/ml) and IL-2 (200 IU/ml) or PHA, IL-2 and peptide LQGV (SEQ ID NO:1) (10 mg/ml) in a volume of 2 ml in six-well plates. After 4 hours of cultures, 10 x 10^6 cells were washed and prepared for ~~genechip~~ GENECHIP® probe arrays experiment. The ~~genechip~~ GENECHIP® array expression analysis was performed according to the manufacturer's instructions (Expression Analysis, Technical Manual, Affymetrix ~~genechip~~ GENECHIP®). The following major steps outline ~~genechip~~ GENECHIP® Expression Analysis: 1) Target preparation 2) Target hybridization 3) Experiment and fluidics station setup 4) Probe Array washing and staining 5) Probe array scan and 6) Data analysis.

Please amend paragraph **[0276]** as follows:

[0276] The ~~genechip~~ GENECHIP® array expression analysis revealed that the LQGV (SEQ ID NO:1) treatment of PM1 (T-cell line) cells for 4 hours in the presence of PHA/IL-2, down-regulated at least 120 genes, more than two-fold as compared to control PM1 cells (stimulated with PHA/IL-2) only. Moreover, at least six genes were up-regulated more than two-fold in peptide-treated cells as compared to control cells.